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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

guidelines for the clinical evaluation of

Antacid Drugs

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Food and Drug Administration

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GUIDELINES FOR THE CLINICAL EVALUATION OF ANTACID DRUGS

April 1978

Comments on the contents of this publication are invited and should be addressed to the following office:

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ABSTRACT

The Food and Drug Administration, with the assistance of its scientific Advisory Committees and other outside consultants, the American Academy of Pediatrics' Committee on Drugs, and consultants to the Pharmaceutical Manufacturers' Association has developed guidelines for the clinical evaluation of new drugs. These guidelines present acceptable current approaches to the study of investigational drugs in man, and pertain to Phases I through III of the investigation. They represent generally accepted principles for arriving at valid conclusions concerning safety and effectiveness of new drugs, as well as the views of outstanding experts concerning appropriate methods of study of specific classes of drugs.

The FDA welcomes comments on the guidelines, and expects to keep them current by review and update at approximately two-year intervals.

FOREWORD

The purpose of these guidelines is to present acceptable current approaches to the study of investigational drugs in man. These guidelines contain both generalities and specifics and were developed from experience with available drugs. It is anticipated that with the passage of time these guidelines will require revision. In order to keep them current a re-review will be performed approximately every 18 to 24 months.

These guidelines are not to be interpreted as mandatory requirements by the FDA to allow continuation of clinical trials with investigational drugs or to obtain approval of a new drug for marketing. These guidelines, in part, contain recommendations for clinical studies which are recognized as desirable approaches to be used in arriving at conclusions concerning safety and effectiveness of new drugs; and in the other part they consist of the views of outstanding experts in the field as to what constitutes appropriate methods of study of specific classes of drugs. In some cases other methods may be equally applicable or newer methods may be preferable, and for certain entirely new entities it is possible that the guidelines may be only minimally applicable.

Under FDA regulations (21 CFR 10.90(b)) all clinical guidelines constitute advisory opinions on an acceptable approach to meeting regulatory requirements, and research begun in good faith under such guidelines will be accepted by the Agency for review purposes unless this guideline (or the relevant portion of it) has been formally rescinded for valid health reasons. This does not imply that results obtained in studies conducted under these guidelines will necessarily result in the approval of an application or that the studies suggested will produce the total clinical information required for approval of a particular drug.

Many of the clinical guidelines have been developed largely, or entirely, by FDA's Advisory Committees and consultants. Others were originally developed by intramural committees and consultants of FDA and of the Pharmaceutical Manufacturers Association; in these cases the guidelines were reviewed and revised, as appropriate, by FDA's Advisory Committees.

The general guidelines for the evaluation of drugs in infants and children and most of those for study of various drug classes in children were developed by the Committee on Drugs of the American Academy of Pediatrics (AAP). Some of the pediatric guidelines for specific classes were written by FDA's Advisory Committees. There was cross review and comment on the pediatric guidelines by both the Committee on Drugs of the AAP and FDA's Advisory Committees.

The Bureau of Drugs of the FDA wishes to thank the many individuals who devoted so much time and effort to the development of these guidelines.

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"General Considerations for the Clinical Evaluation of Drugs" is an important companion piece and should be reviewed prior to reading these guidelines. It contains suggestions which are applicable to investigational drug studies for most classes of drugs and enables elimination of repetitious material in each of the specific guidelines.

I. INTRODUCTION

Definition--A gastric antacid is defined as an agent that will neutralize or remove acid from gastric contents. Both in vitro and in vivo tests must be considered in defining antacids. Under in vitro conditions, antacids must contain at least 5 meq of acid-neutralizing capability in the minimal recommended dose. Such a dose must increase the pH of a suitable system to 3.5 within 10 minutes. There also must be evidence that the agent is effective in vivo as determined by effects on basal gastric content, gastric content after stimulation (e.g., after the administration of pentagastrin), or gastric content after meals.

II. PHASE I STUDIES

A. Variables Appropriate for Study--In Phase I studies the following aspects of gastric acidity might be considered for study:

1. Intragastric pH during basal conditions, nocturnal periods, after stimulation with pentagastrin, or during and after a meal
2. Titratable gastric acidity under conditions as in 1, above
3. Rate of gastric emptying
4. Presence or absence of acid rebound
5. Buffering capacity of gastric content after antacid doses at timed intervals
6. Levels of immunoreactive gastrin in serum

B. Types of Antacids--The types of antacids that will be used in Phase I studies will generally fall into the following categories:

1. Aluminum-containing antacid
2. Bismuth-containing antacid
3. Calcium-containing antacid
4. Magnesium-containing antacid
5. Bicarbonate-containing antacid
6. Mixtures of above
7. Other, to be specified

C. Procedures for Documenting Mechanism of Action or Symptom Relief--If a specific mechanism of action is proposed for the antacid, which is claimed to increase the

efficacy of the agent, the mechanism must be clearly stated and documented by appropriate procedures. If no mechanism of action other than neutralization is proposed, this should be clearly stated. If the antacid is directed toward the relief of symptoms (usually pain or heartburn), the symptom should be defined clearly and the relief therefrom documented as rigorously as possible. In our present state of knowledge, it cannot be inferred that relief of pain by an antacid is dependent upon its acid-neutralizing properties. The possibility that effects on motor activity contribute to pain relief remains, and the presentation of data to elucidate the pharmacologic effects of antacids in the relief of pain should be encouraged.

Examples of the types of specific objective measurements that could be made to document specific claims include monitoring intragastric pH with telemetering capsules or intragastric glass electrodes, determining titratable gastric acidity by sequential aspirations or by intragastric titration with alkali, determining gastric emptying by aspirating labeled meals or by scintigraphy, and quantitation of buffering capacity after meals.

A claim that the antacid accelerates healing of esophagitis or peptic ulceration should be documented by endoscopic studies with or without photographs (and with or without another observer) and, in the case of peptic ulcer, radiographic evidence of disappearance of ulcer craters. The relief of symptoms such as heartburn or the pain of peptic ulcer should be documented in appropriately controlled studies. Claims that properties of antacids such as speed of neutralization, "reactivity," ability to adhere to mucosa, "floating" properties, and others increase the efficacy of antacids should be supported by evidence that pain is relieved better or that healing occurs more rapidly.

D. Drug Effects Other Than the Specific Effects Under Study--In addition to neutralizing gastric acidity, antacids influence transit through the gastrointestinal tract and secretion by the digestive glands. They may also affect the absorption of other drugs. Therefore, the number of daily bowel movements, stool weight, gastric emptying time, lower esophageal sphincter pressure, gastric acid secretion (acid rebound), pancreatic secretion, and the release of gastrointestinal hormones such as gastrin (and others as radioimmunoassays become available) should be determined.

It is not necessary to measure all of these variables in all subjects studied in Phase I; however, it is imperative that a sufficient number of subjects be studied to provide meaningful data.

E. Adverse Effects--Provision should be made for reporting and, if appropriate, measuring all adverse effects. Because the benefit of antacids in treatment is so uncertain, it becomes particularly important that safety be ensured. Periodic reexamination of subjects should be performed at appropriate intervals. There are specific adverse effects that should be looked for with certain types of antacids.

When an absorbable antacid is being used, the specific systemic effects to be looked for are those of metabolic alkalosis. Calcium-containing antacids can produce hypercalcemia, band keratopathy, and impaired renal function. Magnesium-containing antacids may produce hypermagnesemia. Antacids may produce constipation or diarrhea; frequency of bowel movements and daily stool weights are the best means of quantifying these phenomena. Renal stone formation and abnormalities in calcium and phosphate metabolism have been reported. Serum calcium, phosphate, and alkaline phosphatase levels and urine calcium and phosphate levels should be determined in selected subjects. Because antacids interfere with the absorption of some drugs such as tetracycline and clindamycin, evidence of this and other drug interactions when appropriate should be sought in Phase I subjects already taking antibiotics for prophylactic purposes. Obstruction of the gastrointestinal tract due to antacids has been reported. Obstruction as a

result of an unsuspected stricture or narrowing of the lumen should be given particular attention.

F. Subjects

1. Subjects Appropriate for Study--Women with childbearing potential (including nursing mothers) should be excluded. The number of subjects studied should be adequate to provide answers valid at reasonable statistical confidence levels to the specific questions being asked. Normal, healthy, middle-aged males would be appropriate subjects, considering the age group likely to be treated. Patients with healed asymptomatic duodenal ulcers might be suitable subjects in order to ensure a supply of gastric hypersecretors for evaluation of acid neutralization. In addition, subjects receiving prophylactic antibiotic treatment might be included to determine effects of antacids under carefully controlled conditions. Protocols should indicate the sources from which the subjects are drawn.

2. Exclusion

   a. Acute gastrointestinal disorder within the past 30 days

3. Description of Study Population--Acurate description of the sample studied is needed. All subjects screened by the investigator for inclusion in the study and not accepted should be recorded with the reasons for rejection. Characteristics of the study population with respect to age, sex, health status, and any other relevant variables should be recorded. The number of subjects included in the Phase I study should be restricted to that necessary for obtaining the required data.

G. Pretreatment Procedures

In addition to the usual "safety" laboratory studies, laboratory studies appropriate for the drug under study and pretreatment physical examination, the following should be performed and described:

1. Gastric Acidity Studies--Appropriate methods for determining the acidity of gastric contents should be selected. The techniques selected should be used uniformly in all subjects in whom gastric acidity studies are carried out in all phases of the drug trial studies. Possible methods include monitoring of gastric pH by means of intragastric telemetering capsules or intragastric glass electrodes, determination of the titratable gastric acidity by means of serial sampling of gastric contents, or intragastric titration to a constant pH with alkali. It is particularly important to determine the duration of effective neutralization. Nocturnal gastric acidity and acidity after a meal may have particular significance in peptic ulcer disease. Effects on gastric acidity after stimulation with drugs or hormones may provide useful information.

2. Other Procedures--Fasting of subjects and other necessary preparations should be specified.

   Pretreatment workup should be performed in close proximity to the initiation of the drug study.

H. Treatment Period

1. Medication--All drugs utilized in the study, including gastrointestinal motility-modifying agents, must be described and the description must include dosage, dosage forms, and other relevant data for identification.

2. Dosage--The amount per dose and the number of doses of all drugs administered should be recorded.

3. Administration--The method of administration (routes) and the frequency of administration should be recorded.

4. Dose-Response--Once the safety level in single-dose studies is established, a dose-response curve may be constructed for incremental doses with sequential stepwise increases in dosage or other appropriate experimental design taking cognizance of the problem of fade.

5. Observations During Treatment

   The onset of action, the pharmacologic action, and the duration of action of the drug should be recorded.

   a. Pharmacologic Action

      (1) The claimed pharmacologic action should be documented by an appropriate method.

      (2) Data (preferably quantitative) on pharmacologic action should be in a form that can be subjected to statistical analysis.

      (3) It is unacceptable to extrapolate or extend the claimof pharmacologic action beyond that demonstrated.

   b. Serum Levels of Drug

      If appropriate, one may consider studies during Phase I or Phase II which would attempt to correlate, if possible, specific blood levels, with specific changes in gastrointestinal motor activity or relief of symptoms.

III. PHASE II STUDIES

A. Purpose

The purpose of these studies is to determine whether symptoms or alteration in gastric acidity or both differ in patients treated with the test drug and those treated with placebo or another reference drug in one or more of the following conditions:

1. Esophagitis
2. Erosive gastritis or "stress" ulcer
3. Gastric ulcer
4. Duodenal ulcer
5. "Functional" upper gastrointestinal syndromes
6. Other, to be specified

B. General Statements

1. Definition of Clinical Conditions--Because all of the above clinical conditions are listed in these guidelines, each must meet certain specific diagnostic criteria to be included in Phase II studies. Admission to the clinical trial must be restricted to patients in whom the diagnosis is unequivocal. In some of these clinical conditions, biopsy or cytologic examination may be appropriate to exclude malignancy.

a. Esophagitis--The diagnosis will be based on the presence of erosions or ulcers on endoscopic examination with or without documentation by endoscopic photography or another observer.

b. Erosive gastritis including "stress" ulcer--The diagnosis will be based upon the presence of multiple erosions or superficial ulcers on endoscopic examination with or without documentation by endoscopic photography or another observer.

c. Gastric ulcer--The diagnosis will be based on endoscopic or radiographic evidence of crater.

d. Duodenal ulcer--The diagnosis will be based on endoscopic or radiographic evidence of crater.

e. "Functional" gastrointestinal syndromes (idiopathic dyspepsia)--The diagnosis will be based on a clinical picture of symptoms referable to the upper gastrointestinal tract in the absence of significant gastrointestinal disease but with negative upper gastrointestinal radiographic studies, negative endoscopy, negative cholecystograms, and the absence of other gastrointestinal disease.

f. Other conditions--The diagnosis of clinical conditions in the miscellaneous group will be based on the demonstration of gastric acid hypersecretion as well as on specific diagnostic criteria to define the clinical entity.

2. Evidence of Effectiveness

a. Demonstration of neutralization or removal of hydrogen ions from gastric content.

b. Demonstration of rate and extent of healing of mucosal erosions and ulcers--In patients in whom the rate and extent of healing are to be followed, these determinations may best be made by endoscopy but, in the case of gastric and duodenal ulcers, radiologic demonstration of an ulcer crater cannot be excluded as a valid method.

When endoscopic or radiologic techniques are used to follow rate of healing, an objective reference device (calibrated tip of biopsy forceps included in endoscopic picture or a radiopaque device of known dimensions shown on roentgenogram) may be helpful.

c. Relief of symptoms--Partial or complete relief of previously defined specific symptoms will be evidence of effectiveness but the uncertainties in regard to the relationship between acid-neutralizing properties and the ability to relieve symptoms should be borne in mind. In some patients, antacids may be compared with similar preparations of low acid-neutralizing capacity because relief of symptoms may correlate best with as yet undetermined actions of the agent.

d. Improvement in other indices--Improvement in acceptable predefined specific indices (freedom from recurrent attacks of ulcer activity, hospital stay, days lost from work, time of return to usual life style, avoidance of surgery, absence of pain during acid infusions, morbidity, etc.) will also be accepted as evidence of efficacy.

C. Patients

Patients with one of the various clinical entities included in these guidelines and who meet the diagnostic criteria listed in III.B.1 will be appropriate for inclusion in the clinical trial. Thus, the clinical studies will be performed in specific target populations. If pain is to be evaluated, there should be a compatible history for the clinical condition of at least 2 months duration and definite pain should be present on at least 2 of the 3 days preceding the test. Patients with cardiorenal disease in a stable state but requiring antacids for defined clinical conditions may be considered for inclusion in the study to permit evaluation of the role of sodium- and potassium-containing antacids in contributing to retention of fluid and electrolytes under controlled conditions.

The protocol should indicate the sources from which the patients are drawn.

Patients are to be excluded under any one of the following conditions:

1. Occurrence, within 30 days before the initiation of the drug trial, of complications that provide a compelling indication for surgical operation

2. More than one of the clinical conditions under consideration unless such patients are equally distributed in drug and placebo groups

3. Gastric or duodenal ulcers attributable to specific causes (e.g., gastrinoma) unless such patients are equally distributed and stratified for statistical analysis in the drug group as well as in the placebo or reference drug group

4. Concomitant disease or therapy contraindicating trial with drug

5. Chronic alcoholics, drug abusers, or other persons whose reliability and physical status prevent proper evaluation of a drug trial, unless this is the target population to which the therapy is directed

Accurate description of the sample studied is needed. All subjects screened by the investigator for inclusion in the study and not accepted should be recorded with the reason for rejection. Characteristics of the study population with respect to age, sex, health status, and any other relevant variables should be recorded

D. Pretreatment Procedures

In addition to the usual physical examination and laboratory studies appropriate to the drug under investigation, the pretreatment workup should include procedures necessary to establish or confirm the diagnosis. It should be performed in close proximity to the initiation of the drug study.

1. Endoscopy should be performed by an experienced endoscopist (not a person in training). It is highly desirable that the same endoscopist do all of the endoscopic procedures on the same patient. Objectivity will be enhanced if a second observer records his findings independently at the same examination or if findings are documented photographically.

2. Radiologic examinations should be performed by an experienced radiologist. It is advisable for the same radiologist to do all the radiologic procedures on the same patient.

3. Gastric acidity studies should be appropriate to evaluate neutralization of gastric acidity.

4. Other special procedures should be performed as indicated by the chemical composition of the test drug and the clinical condition under study.

E. Study Design

The randomized plan should provide for stratification or a separate protocol according to the types of clinical conditions being investigated with specific grouping of symptoms to be treated. The following should be observed:

1. The target symptoms, laboratory indices, and other special procedures to be studied should be clearly specified.

2. A double-blind stratified and randomized design of drug studied in parallel against a placebo is most desirable. A reference drug of proven efficacy may be appropriately used in some studies.

3. Excluded patients should be accounted for.

4. Dropouts and discontinued patients should be followed up and reported.

5. Other treatment should be applied as uniformly as possible.

6. The crossover study design could be used when appropriate.

7. Appropriate statistical analyses of results as related to the originally stated target symptoms and other observations should be performed.

F. Treatment Period

1. Duration of Trial--The duration of the treatment period should be related to the objectives of the protocol.

2. Medication--Treatment is begun on the day after completion of the workup. Subjects are randomly assigned to the study groups. The methods of random assignment should be specified in detail.

   a. Dosage

      (1) Dose schedule should be established before the study starts, and changes in dosage during the clinical trial should be avoided except when untoward effects occur.

      (2) Alternatively, different fixed dose levels may be assigned in the treatment group(s). Variation or adjustment of dosage for individual patients on the basis of symptom response alone is not encouraged.

   b. The placebo should be indistinguishable in form from the test drug and administered on the same predetermined schedule.

   c. If a reference drug is used, this also should be indistinguishable in form from the test drug and administered on the same predetermined schedule.

   d. Other drugs--Patients should be advised not to take salicylates, analgesics, other antacids, sedatives, stimulants, or tranquilizers. Since the patients probably will not follow this advice completely, the agents and the amounts used should be recorded. Failure to follow this advice is not necessarily grounds for exclusion from the study. When other drugs must

be prescribed, the specific drugs and the amounts used should be documented.

3. Diet--No specific diet need be prescribed apart from avoidance of those foods that tend to exacerbate the symptoms. A daily diet diary is recommended.

4. Setting--Patients included in the study should be in one of the categories:

   a. Hospitalized

   b. Outpatient

   c. Fixed ratio, such as 1 week or less in the hospital and 2 weeks or more as an outpatient

5. Observations During Treatment

   a. Toxicity--Evaluation of the toxicity of the drug under study should be carried out with appropriate observations and laboratory tests performed at specified intervals. Mechanisms for early detection of toxicity as manifested by signs, symptoms, or laboratory evidence must be built into the protocol. Specific procedures for withdrawal of the patient from the study because of toxicity should be stated in the protocol.

   b. Withdrawal of patients from trial by physician

      (1) Withdrawals will be made for reasons of toxicity or when deemed clinically appropriate because of changes in severity of illness, development of complications, or life-threatening aspects of the clinical entity being studied.

      (2) There should be preestablished criteria for withdrawals.

      (3) The reasons for withdrawals should be concisely identified.

      (4) Patients withdrawn from the study should be followed until resolution of the condition requiring the withdrawal.

      (5) Results should be analyzed in three groups: (a) all who started on study including those who withdrew, (b) only those who completed study, and (c) only those who withdrew from study.

   c. Indices of effectiveness--The observations required for those indices of effectiveness that have been selected for study should be carried out at specified intervals and recorded systematically during the study. These indices include but are not restricted to gastric acidity methods, endoscopic and radiologic evaluations, gastric secretory studies, symptom analysis, and time lost from work, etc.

      Selected procedures and laboratory determinations may have to be repeated several times during the treatment period in order to detect cumulative effects or the development of tolerance.

      Daily diary or evaluation sheets should be kept by the patient during the treatment period.

There should be uniform periodic visits to the physician with recorded evaluations (rating scales, etc.) until a predetermined end point has been reached.

G. Observations After Treatment

Appropriate follow-up observations should be made in order that possible delayed adverse effects are not overlooked.

H. Data Analysis

Appropriate statistical analyses of results as related to the originally stated target symptoms, laboratory tests, and special procedures should be done.

The protocol should state in advance what will be considered evidence of effectiveness, keeping in mind that statistical significance is not necessarily clinical significance. All data pertaining to indices of efficacy should be recorded on forms designed for that purpose and specified in the protocol. Diaries, symptom-rating scales, and physician and patient assessment forms should be used as appropriate. These should be pretested and shown to be workable before the study is begun.

The method of scoring each index of effectiveness should be clearly defined in the protocol. The method(s) of statistical analysis of the scores of each index should be clearly stated in the protocol, with literature references. (An acceptable model for a grading scale would be: 0 = none; 1 = present but patient able to carry on usual activities; 2 = interferes with usual activities; 3 = disabling.) Keeping the number of grades as few as possible facilitates the assessment.

Analysis of results should be carried out in such a way as to first include and then exlude withdrawals; results for withdrawals alone also should be analyzed. Withdrawals include patients who withdrew from the study on their own as well as patients dropped from the study by the investigator for failure to comply with the protocol (defined here as failure to take the test drug). Patients who do take the drug but use other medications or substances or diets that are not prescribed by the protocol should be grouped separately and included.

I. Effectiveness Standards

Clinical studies should be done in specific populations that meet specific diagnostic criteria. Appropriate stratification within each specific diagnostic category should be carried out at the time of data analysis to delineate efficacy of the test drug in the setting of varying degrees of severity of the disorder. In some instances, it may be advisable to stratify patients as to age, sex, and duration of disease before randomization. In addition to data obtained pretreatment and during treatment, any preexisting condition that might bias analysis, such as gastroesophageal reflux, should be taken into consideration in the analysis of data. Efficacy can also be shown by comparison of effects of a placebo or reference drug with those of the drug to be tested in the same patients as well as between groups of patients. Although a study design in which a patient serves as his own control may sometimes be used to demonstrate effectiveness of a new agent, if such study design is used it is essential to allow an adequate interval between the drug and placebo treatment periods so that all indices under study may return to baseline levels. The duration of this interval will be determined by the compound being used, the clinical condition, and the indices under observation.

Two criteria must be met for a new drug to be classified as an effective antacid:

1. By appropriate in vitro and in vivo methods it must be documented that the test drug does indeed neutralize or remove hydrogen ion from gastric contents in significant quantities. It should act within a reasonable time and its effect should last long enough to be compatible with an acceptable dosage schedule.

2. The drug must be shown to effect improvement in acceptable, specific, predefined indices.

IV. PHASE III STUDIES

This represents extension of Phase II to include patients treated for longer periods (determined by the natural course of the clinical entity and patterns of recurrence when appropriate) to evaluate increased risks, to detect complications, and to explore safety and efficacy under conditions of clinical practice. In this Phase, it is not necessary to perform gastric secretory studies in patients with specific clinical entities. Appropriate indices of clinical evaluation, including physical examinations and laboratory tests, should be monitored to detect evidence of toxicity. To demonstrate additional significant evidence of efficacy, appropriate clinical studies should be designed and performed.

The ABSTRACT CARDS below are designed to facilitate document retrieval using Coordinate Indexing. They provide space for an accession number (to be filled in by the user), suggested keywords, bibliographic information and an abstract.

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FDA welcomes comments on the guidelines, and expects to keep them current by review and update at approximately two year intervals.
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